Individual-based Force-based model of Tumour Growth

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## Why Model Cancer?

### Lifetime risk

- **50%**
- 1 in 2 UK people will be diagnosed with cancer in their lifetime

### Cases

- **359,960**
- New cases of cancer, 2015, UK

### Proportion of UK deaths

- **28%**
- Cancer causes more than one in four of all deaths, 2016, UK

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**Number of new cases in 2018, both sexes, all ages**

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>2,093,876</td>
<td>11.6%</td>
</tr>
<tr>
<td>Breast</td>
<td>2,088,849</td>
<td>11.6%</td>
</tr>
<tr>
<td>Colorectum</td>
<td>1,849,518</td>
<td>10.2%</td>
</tr>
<tr>
<td>Prostate</td>
<td>1,276,106</td>
<td>7.1%</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>569,847</td>
<td>3.2%</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>572,034</td>
<td>3.2%</td>
</tr>
<tr>
<td>Liver</td>
<td>841,080</td>
<td>4.7%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>18,078,957</strong></td>
<td></td>
</tr>
</tbody>
</table>

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**Immunotherapy in pancreatic cancer: New hope or mission impossible?**
- *Cancer* Letters, Volume 445, 31 March 2019, Pages 57-64
  - Jiahong Jiang, Huaxiang Zhou, Chao Ni, Xiaoge Hu, ... Liu Yang

**The Untranslated Regions of mRNAs in Cancer**
- Trends in *Cancer*, in press, corrected proof, Available online 22 March 2019
  - Samantha L. Schuster, Andrew C. Hsieh

**Mutagenic players in ALL progression and their associated signaling pathways**
- *Cancer* Genetics, Volumes 233–234, April 2019, Pages 7-20
  - Saadiya Zia, Ramla Shahid

**Skin cancer: Missing eyelids when using SPF moisturiser a 'risk'**
- BBC News - 11 hours ago
  - Failing to apply moisturiser with sun protection factor (SPF) and sunscreen properly to the face, particularly around eyes, could be putting ...

**A bottle of wine a week could increase women's cancer risk as much as smoking 10 cigarettes**
- The Telegraph
What’s the problem and how can we help?

Cancer:
- multitude of bodily diseases
- cells do not behave normally
- can arise from any type of cell
- can grow in or around any tissue or organ

Tumour cells:
- proliferate and occupy whole areas of tissue
- interact with surrounding cells, tissue structures, vasculature and the extracellular matrix

Treatment for cancer:
- target tumour cells
- have limited/no effect on the surrounding healthy cells and environment

**in silico** experiments complement traditional biological and experimental approaches to cancer research.
The Hallmarks of Cancer


~90% of cancer deaths attributed to metastases
The Tumour Microenvironment

- simulate spatio-temporal interactions between cells, fibres and blood vessels
- 3D individual-based force-based model
  i.e. each element is fully realised and interactions are primarily governed by mechanical forces
Each cancer cell is an agent which:
- grows and divides
- [acquires phenotypic profiles]
- interacts with other cells, vessels and extra-cellular matrix

**Equation of Motion**

\[
\Gamma \ddot{x}_i(t) + a^r f_i(t) = \sum F(t)
\]

friction \hspace{1cm} \text{random} \hspace{1cm} \text{forces}

\[
x_i(t^{n+1}) = x_i(t^n) + \frac{\Delta t}{\gamma} \left( -a^r f_i(t^n) + \sum F(t^n) \right)
\]
Cell-cell Interactions

\[ \sum_{j=1}^{N_{\text{cells}}} F_{ij} \]

\[ F_{ij} = \left\{ \frac{4}{3} ER_{ij}^2 h_{ij}^3 - \alpha \left( R_i - \frac{h_{ij}}{4} \right) h_{ij} \right\} \frac{d_{ij}}{||d_{ij}||} \]

repulsion

adhesion
Cell-cell Interactions

higher birthrate
Cell-cell Interactions

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Cell-cell Interactions

$$F_{ij} = \left\{ \frac{4}{3} E R^\frac{1}{2} h_{ij}^3 - \alpha \left( R_i - \frac{h_{ij}}{4} \right) h_{ij} \right\} \frac{d_{ij}}{||d_{ij}||}$$

lower adhesion
Cell-cell Interactions

$$F_{ij} = \left\{ \frac{4}{3}ER^{\frac{1}{2}}h_{ij}^{\frac{3}{2}} - \alpha \left( R_i - \frac{h_{ij}}{4} \right) h_{ij} \right\} \frac{d_{ij}}{||d_{ij}||}$$

lower repulsion
Cell-vessel Interactions

Mechanical interactions:

\[ F_{i,v} = \left\{ \frac{4}{3} \hat{E} R_i^{\frac{1}{3}} h_{iv}^{\frac{2}{3}} - \alpha_{\text{vessel}} \left( R_i - \frac{h_{iv}}{4} \right) h_{iv} \right\} \frac{d_{iv}}{||d_{iv}||} \]

concentration: blue (low) - red (high)
Cell-vessel Interactions

\[ \partial_c \frac{\partial c}{\partial n} = 1 \int_v \left( c_v - c \right) \text{ on } \partial \Omega \]

\[ \partial_c \frac{\partial c}{\partial n} = 1 \int_v \frac{\alpha_n \rho_n(t_m) + \alpha_h \rho_h(t_m)}{c(T) + c(t_m-1)} \text{ on } \partial \Omega_v \]

\[ \frac{\partial c}{\partial n} = \frac{1}{J_v} (c_v - c) \text{ on } \partial \Omega_v \]

\[ \frac{\partial c}{\partial n} = \frac{1}{\eta D_{O_2}} (c_{+\infty} - c) \text{ on } \partial \Omega / \partial \Omega_v \]

Oxygen Concentration

concentration: blue (low) - red (high)
Cell-vessel Interactions
Cell-vessel Interactions

Cells acquire phenotypic profiles:
- Normoxic cells - sufficient oxygen
- Hypoxic cells - low oxygen
- Dead cells - insufficient oxygen

Dead cells:
- biologically inactive
- move only as a consequence of mechanical forces

Hypoxic cells:
- activate anaerobic metabolism
- stop proliferating
- acquire additional motility
- may revert to normoxic

\[
\frac{\alpha_n \rho_n + \alpha_h \rho_h}{c(T) + c}
\]
Hypoxia is what makes cancer dangerous!

Cell-vessel Interactions

colour indicates phenotype (red - normoxic, blue - hypoxic, black - dead)

dead cells
Cell-fibre Interactions

Mechanical interactions:

\[ \mathbf{F}_{if} = \alpha_{\text{fibre}} \left( 1 - \frac{\|\mathbf{v}_i\|}{v_{\text{max}}} \right) \left( \frac{\langle \mathbf{v}_i \cdot \mathbf{l}_f \rangle}{\|\mathbf{v}_i\|} \right)^p \mathbf{l}_f \]

\[ -\beta_{\text{fibre}} \left( \frac{\|\mathbf{v}_i\| - \mathbf{v}_i \cdot \mathbf{l}_f}{\|\mathbf{v}_i\|} \right)^q \mathbf{v}_i \]

Credit: cellbiology.med.unsw.edu.au
Cell-fibre Interactions

blue cell - original cell
Cell-fibre Interactions
Cell-fibre Interactions
Cell-fibre Interactions
Cell-fibre Interactions

Blue fibres have been degraded
**Current Code**

- **Cells**: different phenotypes, genotypes could incorporate normal cells, immune cells

- **Vessels**: tumour wraps around/embeds within vasculature - any geometry.

- **Fibres**: "cancer" cells move within tissue affected by the local environment

Credit: Bumsoo Han, Kinam Park, Murray Korc, Purdue University

Credit: Vakoc et al., Nature Medicine, 2009

Credit: Friedl & Alexander, Cell, 2011
There is A LOT more to do…

Future Directions

Model diffusion of other key chemicals:
- VEGF (vascular endothelial growth factor) signal angiogenesis
- MMPs (matrix metalloproteinases) degrade the extracellular matrix

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Link to angiogenesis model

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Model drug delivery and processes:
- affect on the tumour and local environment
- best delivery method
- optimum dosage

Improve cell collective migration properties:
- follow the leader behaviour
- chemotaxis/haptotaxis
Future Directions

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blue follower cells; red leader cell
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  - intravasation
  - extravasation

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- Link to angiogenesis model

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Future Directions

Model important metastasis processes:
- intravasation
- extravasation

- Model how cells are polarized due to their local environment and how they gather and move collectively (invasion).
- Connect model to model of angiogenesis.
- Simulate the process of intravasation of cancer cells into the local blood vessels and then the reverse, extravasation, at a secondary site (metastasis).

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Link to angiogenesis model

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Work out ways to control cancer!
Thank you